Office Action Summary	Application No.	Applicant(s)	
	09/469,733	ETTER, JEFFREY B.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48 and 77-86* is/are pending in the application.

4a) Of the above claim(s) *none* is/are withdrawn from consideration.

5)☒ Claim(s) *28, 30-31, 33-36, 45-47 and 78-86* is/are allowed.

6)☒ Claim(s) *1-27,29,32,37-44, 48 and 77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment 18 July 2003 (Paper No. 23) as to amendment of claims 1, 3 10-13, 17, 38-40 and 46-47, cancellation of claims 49-76 and addition of claims 77-86, and applicants' request for exertion of time of three months filed 18 July 2003 (Paper No. 22) have been entered. Thus, claims 1-48 and 77-86 are pending to which the following is or remains applicable.

Please note that grounds of objection and/or rejection not explicitly restated and/or set forth below are withdrawn.

Claim Rejections - 35 USC §102

The previous rejection under 35 USC 102 (b) is withdrawn

The previous rejection under 35 USC 102 (b) over Manning et al. patent is withdrawn because applicant added to claim 1 of the current application the limitation "separating the particles from the first solvent …", which obviates the rejection.

The following is the new ground(s) of rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-2, 7-13, 19-20, 22-23, 25-27 and 38-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Sievers, R. E. (US Pat. No.5639441).

Sievers teaches a method of producing a drug particle (including insulin, see the patent claim 20) comprising contacting the first fluid containing the drug and cosolvent and the second fluid, which is any organic solution that is insoluble or only partially soluble in the first fluid (especially see column 6, lines 2-4), with an antisolvent supercritical fluid and precipitating (i.e., separating) the particle from the fluids (see abstract, column 5, line 66 to column 6, line 56, and column 7, lines 17-20), which meets the limitations set forth in claims 1-2.

Sievers teaches that the fluid are mixed; the mature comprises the first and the second fluids (see column 6, lines 5-8), and that the first fluid comprises surfactant (see the patent claim 11). Also, Servers teaches that the fluids may contain surfactants, co-solvents, anti-solvents, and other components (see column 6, lines 53-55) and that the particles also comprise surfactant (see the patent claim 21), indicating the particles are multi-component articles including insulin (the patent claim 20), e.g., biopolymer lipid. The above Sievers' teaching meets the limitation set forth in claim 20.

Sievers teaches that the first fluid is dimethyl sulfoxide (see column 6, line 51) and that the second fluid is any organic solution that is insoluble or only partially soluble in the first fluid (especially see column 6, lines 2-4). Also, Sievers teaches that the second fluid is ethanol (see column 6, lines 25-40) which is a supercritical fluid (column, lines 25-26). The Servers' teachings are applied to the application claims 7-9 and 38.

Sievers teaches the reduced pressure for precipitating the drug particle (see column 6, lines 1-20), a critical pressure of 1072 psi (see column 6, lines 45-46) and applied pressure 750 psi (see column 13, line 21); thus, the ration of the reduced pressure would be 1000/1072 =0.93 which is larger than 0.8. Also, Sievers teaches the temperature ratio of the applied T = 40°C to

the critical temperature 31.3 °C (see Example 2 and column 6, line 44) that gives rise to the ratio 40/31.3 = 1.27, which value is larger than 0.95 (note that 40 °C is obtained from an average of the values 20°C and 60°C of Example 2). Thus, the Sievers' teaching is applied to claims 10-11 and 39-41 of the instant application.

Sievers teaches that supercritical fluid precipitation (see column 3, line 67 to column 4, line16), and that a compressed supercritical fluid is carbon dioxide (see the patent claims 1 and 9), as applied to claims 12-13 and 42-44 of the instant application.

Sievers teaches that the desired substance is present in an emulsion (i.e., colloidal) form (see column 4, lines 17-21, and column 5, lines 57-60), as applied to claim 19 of the instant application.

Sievers teaches that the first fluid is ethanol (see column 6, line 51), as applied to the application claim 25-27.

Thus, Servers' patent anticipates 1-2, 7-13, 19-20, 22-23, 25-27 and 38-44 of the current application.

Claim Rejections - 35 USC §103

Note that the following is the new ground of rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 7-13, 15, 19-27, 29, 32, 37-44, 48 and 77 are rejected under 35 U.S.C. 103(a) as being obvious over Manning, M. C. *et al.* (US Pat. No. 5770559) taken with Sievers R. (US Pat. No. 5639441), Debenedetti P. G. *et al.* (US Pat. No. 6063910) and Pace, G. W. et al. (US Pat. No. 6177103).

Manning *et al.* teach a method for making particles including a pharmaceutical material, *e.g.*, insulin, (see claim 30, column 5, lines 41-63 and Table 1 at column 18) wherein the particles are recovered in a powder form for direct pulmonary delivery (see claim 1 and examples 13 and 17), the method comprising the steps (*outlined in Figure 12*) of: (1) contacting the feed solution with the anti-solvent in order to precipitate the solid particles containing pharmaceutical polypeptide, *e.g.*, insulin (see claims 1 and 30), and (2) separating the resultant particles (see column 11, lines 31-52, and column 12, lines 43-60). Manning *et al.* describe the characteristics of the feed solution that contains: *a*) pharmaceutical substance (*e.g.*, insulin), *b*) organic solvent-I (*e.g.*, sodium dodecylsulphate) that dissolves the pharmaceutical substance, *c*) organic solvent-II (*e.g.*, dimethyl formamide), wherein *b*) and *c*) are mutually soluble (see column 11, lines 33-37) referring to a "co-solvent system". Also, Manning et al. teach the precipitated particles are separated from the exiting fluid (see column 11, lines 43-46). The Manning *et al.* teaching meets all the limitation of claim 1. Thus, the patent anticipates claim 1 of the current application. Since insulin is much more soluble in sodium dodecylsulphate (organic solvent-I) than in hexane (organic solvent-II) (see Table I, at column 18, and column 6, lines 48-57), the Manning teaching is also applied to claim 2 of the current application.

Manning *et al.* teach the organic solvent is ethanol (see Table I, column 18), as applied claims 8-9 of the current application.

Manning *et al.* teach anti-solvent precipitation technique wherein the anti-solvent fluid is at a reduced pressure of 0.8 to ~ 1.2 (see column 12, lines 3-13), as applied to claims 10-11 of the instant application, and teach that the fluid includes carbon dioxide (see column 3, line 1-9, and column 12, lines 14-17) for supercritical processing (see column 12, lines 14-15), as applied to the application claims 12-13 and 42-44.

Manning *et al.* teach a biocompatible polymer co-dissolved with the pharmaceutical substance in the feed solution and incorporated into a powder (see column 3, lines 24-34, and abstract) that contains multiple components: pharmaceutical substance, *e.g.*, insulin (see column 5, lines 63 and claim 30), and biodegradable polymer (see column 14, lines 9-56), as applied to the application claims 20.

Manning *et al.* teach the biopolymer, *e.g.*, a poly [ethylene glyco] (see column 14, lines 41-57, and example 14), sodium dodecylsulphate (organic solvent I) (see column 6, lines 33-47 and 52-53), and ethanol and acetone *etc.* (organic solvent II) (see Table 1). Because it is apparent that insulin peptide is more soluble in sodium dodecylsulphate than in the biopolymer and because the solvent II, i.e., acetone, is a non-polar solvent for the biopolymer, the Manning *et al.* teaching is applied to the application claims 21 and 22.

Manning *et al.* teach that sodium dodecylsulphate [solvent I] is miscible with water and that the organic solvent *e.g.*, CCl_4 and acetone [solvent II] (see Table 1) are immiscible with water, as applied to the application claim 23.

Manning *et al.* teach that the organic solvent (solvent II) is tetrahydrofuran (see column 7, line 12), as applied to the application claim 24.

Manning *et al.* teach methylene chloride as the organic solvent (see Tables 1-2), as applied to the application claim 28, and teach a acid, *e.g.*, poly-glycolic acid dissolved in a volatile organic solvent (see example 14), as applied to the application claim 29.

Manning *et al.* teach prior to contacting of the fees solution to the anti-solvent fluid the pharmaceutical substance is prepared in homogenous solution (i.e., feed solution) (see the patent claims 1 and 12) comprising mixing solvent I having the pharmaceutical substance (e.g., insulin) dissolved and solvent II in which the biopolymer is dissolved (see the patent claim 15), as applied to claim 32 of the instant application.

Manning *et al.* teach the ratio of the biopolymer to insulin is 50:50, as applied to claim 37 of the instant application.

Also, Manning *et al.* teach the antisolvent fluid invades the organic solvent of the liquid feed solution comprising solvent I and II resulting in precipitation of solid particles comprising insulin (see column 11, lines 39-46), as applied to claim 38 of the instant application.

Further, Manning *et al.* teach the poly-lactic acid in the feed solution (see example 14), as applied to claim 48 of the instant application.

In addition, Manning *et al.* teach precipitation of the pharmaceutical substance use an antisolvent fluid which permits processing at relatively mild temperature by contacting technique wherein the feed solution that comprises the solvents I and II is flown into the anti-solvent fluid (see column 12, lines 25-31 and lines 43-56), as applied to the application claims 77.

Manning et al., however, do not teach separating the particles containing insulin from solvent I as the Manning' particles comprise surfactant SDS molecules, neither the limitations as

to (1) the particles being in a colloidal form,; (2) means and conditions (e.g., the reduced critical pressure) of introducing feed solution into the compressed anti-solvent fluid *etc*; and (3) the first solvent is organic solvent (e.g., ethanol) rather than amphiphilic molecule.

Sievers teaches a method of producing a drug particle (including insulin, see the patent claim 20) comprising contacting the first fluid containing the drug and cosolvent and the second fluid, which is any organic solution that is insoluble or only partially soluble in the first fluid (especially see column 6, lines 2-4), with an antisolvent supercritical fluid and precipitating (i.e., separating) the particle from the fluids (see abstract, column 5, line 66 to column 6, line 56, and column 7, lines 17-20), which meets the limitations set forth in claims 1-2. Thus, the Sievers' teaching anticipates claims 1-2 of the instant application.

Sievers teaches that the fluid are mixed; the mature comprises the first and the second fluids (see column 6, lines 5-8), and that the first fluid comprises surfactant (see the patent claim 11). Also, Servers teaches that the fluids may contain surfactants, co-solvents, anti-solvents, and other components (see column 6, lines 53-55) and that the particles also comprise surfactant (see the patent claim 21), indicating the particles are multi-component articles including insulin (the patent claim 20). The above Sievers' teachings are applied to the application claim 20.

Sievers teaches that the first fluid is dimethyl sulfoxide (see column 6, line 51) and that the second fluid is any organic solution that is insoluble or only partially soluble in the first fluid (especially see column 6, lines 2-4). Also, Sievers teaches that the second fluid is ethanol (see column 6, lines 25-40). The Servers' teachings are applied to the application claims 7-9 and 38.

Also, Sievers teaches that the reduced pressure for precipitating the drug particle (see column 6, lines 1-20), a critical pressure of 1072 psi (see column 6, lines 45-46) and applied pressure 750 psi (see column 13, line 21); thus, the ration of the reduced pressure would be 1000/1072 =0.93 which is larger than 0.8. Also, Sievers teaches the temperature ratio of the applied T = 40°C to the critical temperature 31.3 °C (see Example 2 and column 6, line 44) that gives rise to the ratio 40/31.3 = 1.27, which value is larger than 0.95 (note that 40 °C is obtained from an average of the values 20°C and 60°C of Example 2). Thus, the Sievers' teaching is applied to claims 10-11 and 39-41 of the instant application.

Sievers teaches that the second fluid is any organic solvent that is insoluble in the first fluid that is polar solvent (see columns 5-6), as applied to the application claim 18.

Also, Sievers teaches that the desired substance is present in an emulsion (i.e., colloidal) form (see column 4, lines 17-21, and column 5, lines 57-60), as applied to claim 19 of the instant application.

Further, Sievers teaches that the first fluid comprises surfactant (see the patent claim 11), and that the fluids may contain surfactants, co-solvents, anti-solvents, and other components (see column 6, lines 53-55).

Debenedetti *et al.* teach a method for preparing protein microparticles containing the bioactive polypeptide, *e.g.*, insulin (claim 8, column 6, lines 14-17, and Figures 6-7) *via* a compressed anti-solvent precipitation technique (see column 4, lines 54-67), as applied to claims 1 of the current application. Also, Debenedetti *et al.* teach a mean of controlling sample solution contacting with the anti-solvent fluid and precipitation of the sample particle thereof, wherein the

solution is preferably in a form (< 1 mm diameter, i.e., 0.785 mm^2) having a relatively large surface area for immediate exposure to the supercritical fluid for immediate exposure to anti-solvent fluid. The Debenedetti et al. teaching is applied to claim 15 of the current application.

One of ordinary skill in the art would have combined the teachings of the above references to arrive at the current invention stated above. Manning et al. teach the method of preparing particles containing pharmaceutical polypeptide (including insulin) using the anti-solvent technique. Although Manning et al. do not teach separate surfactant SDS from the solvent I, it would have been obvious for the skilled artisan to successfully develop a method of preparing insulin particles based on the Manning method since (*a*) Sievers' patent offers the advantage that the disclosed method is particularly useful for substances which are significantly soluble only in water because transforming aqueous solutions into the supercritical state decomposes most bioactive substance (see column 4, lines 10-16) (please note that insulin is such a peptide soluble in water); and since (*b*) use of surface modifiers without extracting the modifiers into the final prepared particles comprising drug *via* compressed fluid antisolvent process is advantageous over the Manning et al. method in that allows making submicron particles without particle aggregation or flocculation, as taught by Pace et al. patent (see especially column 3, line 67 to column 4, line 3).

In addition, the skilled artisan would have combined the above reference teachings also because (1) Sievers teaches an effective process of precipitating insulin using the fluid comprising surfactant compound, and teaches a mean of emulsion-based preparation of active substance in conjugation with the anti-solvent fluid technique; and (2) the Debenedetti et al.

teach a mean of controlling sample solution contacting with the anti-solvent fluid so as to achieve the desired characteristics of the precipitated particles thereof.

Further, when combined, the above references would have offered the following additional advantages: (1) controllable size of microparticles for drug delivery and microparticle/antisolvent technique disclosed thereof is particularly useful for hydrophobic enzyme or protein of which insulin is a preferred protein (see column 2, lines 23-36), as taught by the Debenedetti *et al.* patent; (2) the compressed antisolvent technique developed by Debenedetti et al. benefits very rapid precipitation of the soluble material, which will result in extremely uniform and fine particle sizes (see column 2, lines 56-60); and (3) co-dissolution of the pharmaceutical substance with a biodegradable polymer reduces the problem of compositional variation or concentration of the substance near the surface of the anti-solvent precipitated particles as taught by Manning et al. (see column 3, lines 24-35).

Based on the above motivation and the advantages, the skilled artisan would have been readily arrived at the current invention as to manufacturing insulin particles based on antisolvent fluid technique. Because both the Sievers teaching (see column 8, lines 35-39) and the Manning *et al.* teaching are directed to pulmonary delivery of the resultant particles and the Debenedetti *et al.* teaching is also directed to drug particles for therapeutic use, the skilled artisan would have a reasonable expectation of success that improves the quality as well as quantity of the interest therapeutic substance formulated in particles for delivery. Thus, the claimed invention was *prima facie* obvious to make and use at the time it was made.

Claim Rejections - Provisional Rejection, Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130 (b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 and 77 of the instant application are provisionally rejected under the judicially created doctrine of double patenting over claims 1-4, 94, 95, 5, 6, 7, 8, 9, 10, 11, 13, 22, 14, 15 and 16 of copending Application No. 09740573. This is a provisional double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 3, 4, 5, 6, 7, 10, 11, 22, 14, 15 and 16 of Application 09740573 are identical to claims 1, 2, 3, 4, 7, 8, 9, 12, 13, 15, 16, 17 and 18 of the instant application except that 09740573 set forth "a drug" while the current application claims set forth "insulin". Because claim 20 sets the limitation to the disclosed drug that "the drug is insulin", the claims of the current application and application 09740573 are obvious variations one another.

Claims 94 and 95 of Application 09740573 sets forth a concentration of the drug dissolved in the cosolvent system; in view of claim 20 that discloses that the said drug is insulin, claims 5 and 6 of the instant application are obvious variation of claims 94 and 95.

Claim 13 of Application 09740573 set forth the same disclosure as that of claim 14 of the instant application except the recitation "the drug" in Application 09740573. because the reason state in the precedence, the claim 13 of 09740573 and claim 14 of the current application are obvious variation each other.

Claims 8 and 9 of Application 09740573 set forth the common subject matter as that of claims 10 and 11 of current application but with different scope.

Claim 22 of Application 09740573 is an obvious variation of claim 77 of the instant application since the claims of both applications are directed to that during contacting step the feed solution comprising the first and the second organic solvents is introduced into the anti-solvent fluid.

Therefore, the claims of the present application are not patentably distinct from the claims of Application No. 09740573.

The response to the rejection under Provisional Rejection, Obviousness Type Double Patenting

Applicants' comment at page 13 of the response filed 18 July 2003 is noted but it is unpersuasive. The rejection is maintained since the assertion "... filing of a terminal disclaimer in the instant application will be considered to address ..." does not remove the ground of rejection nor does it indicate reason why the rejection should be removed.

Conclusion

Claims 1-27, 29, 32, 37-44, 48 and 77 are rejected. Claims 28, 30-31, 33-36, 45-48 and 78-86 are free of the prior art in record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:30 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703-308- -4700.

Samuel Wei Liu, Ph.D.

August 12, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER